II. REMARKS

Status of the Claims

Claims 1-72 remain pending in the case. Claims 4-15, 23-33, 38-49, and 57-68 have been amended to clarify that concentrations are presented in weight/volume percentages. Claim 20 has been amended to more clearly define what the Applicant considers to be the invention. No new matter is added by these amendments, nor is it believed that any subject matter has been surrendered.

Information Disclosure Statement

A new Form 1449 correcting the citation for reference D6 of the IDS filed January 7, 2003 is enclosed together with the appropriate fee. Copies of references D9 and D10 of the IDS filed December 15, 2003 are also enclosed. Consideration of these references is requested.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 4-15 and 23-33 are rejected as being unclear as to whether the percentages are by weight or molar concentration. Claims 4-15 and 23-33 as well as claims 38-49 and 57-68 have been amended to clarify that concentrations are presented in weight/volume percentages. These amendments are supported by the Specification, for example, at page 14, lines 3-11 which discusses various preservatives studied in Example 1, each described as a weight/volume measure, as, for example, "2-phenoxyethanol 0.5% w/v" and "benzethonium chloride 0.01% and 0.02% w/v." These Amendments thus render the Examiner's rejections as moot.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 20, 23-27, and 34 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Kakimoto et al. Claim 20 has been amended to be directed to an erythropoietin pharmaceutical carrier composition to more clearly define what the Applicant considers to be the invention thus rendering the Examiner's rejection moot.

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Nomura et al. Applicant respectfully traverses this rejection.

As stated in the present Specification at page 7, lines 1-4, "[p]rovided are novel EPO-containing multi-dose pharmaceutical formulations containing preservatives that *individually* provide for stable, sterile, easily administered compositions." (emphasis added). Further, the difficulties associated with creating these EPO compositions from the prior art is discussed extensively at page 4, line 1 to page 5, line 5.

As previously discussed, Nomura et al. allegedly discusses the use of benzethonium chloride as a surfactant for oral dose preparations of erythropoeitin in amounts between 0.1 and 1000 parts by weight to one part per weight of erythropoeitin. Since benzethonium chloride is not used in any of the specific examples, it remains unclear whether the compositions disclosed in Nomura would provide stable, sterile, EPO multi-dose compositions. As discussed above, the difficulties of providing stable, sterile, multi-dose EPO compositions were well known and it was not at all obvious that adding benzethonium chloride to EPO compositions would result in effective stable and sterile compositions suitable for multi-dose use. The claimed compositions thus provide an improvement over prior art compositions such as those discussed in the Specification at page 2, lines 14-21 wherein the EPO is degraded, inactivated, forms aggregates, or suffers some other adverse interaction making it unsuitable for use. There is nothing in Nomura to suggest that the compositions disclosed therein would overcome the difficulties discussed above and result in stable, sterile formulations. As Nomura fails to teach each and every element of the present invention, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 4, 5, 7, 8, 16-20, 23, 24, 26, 27, 34-35, 50-54, 57-61, and 69-72 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Strickland et al. in view of Uda et al. and Sandeep et al.

First, the Examiner wrongly asserts that the explicit statement of Strickland cited by the Applicant, namely that "...nothing specific can be derived from the use of preservatives with other proteins that would suggest any particular preserved formulation for erythropoietin," is not found in the Strickland reference. Applicant respectfully directs the Examiner's attention to Column 3, lines 56-58 where Strickland makes the specific statement cited above and further cites to Geigert, J., "Overview of the Stability and Handling of Recombinant Protein Drugs," Journal of Parenteral Science & Technology, Vol. 43, No. 5, 220-224 (1989) for further support. Therefore, as stated previously, Strickland teaches away from the substitution of benzethonium chloride for benzalkonium chloride that the Examiner has suggested.

Further, Uda et al. does not, as the Examiner suggests, teach that benzethonium chloride and benzalkonium chloride are functionally equivalent. Specifically, as discussed previously, Uda et al. mentions benzethonium chloride exactly once when the reference states that "pharmaceutical composition for intranasal delivery may contain a preservative, e.g. p-hydroxybenzoic esters, phenols such as phenol, cresol, etc., alcohols such as chlorobutanol, phenylethyl alcohol, propylene glycol, etc., invert soaps such as benzalkonium chloride, benzethonium chloride, etc." Simply because benzethonium chloride and benzalkonium chloride are both invert soaps does not make them functionally equivalent, particularly in light of the difficulties of providing stable EPO formulations – difficulties addressed by both Strickland and the present Applicant, namely, problems where EPO is degraded, inactivated, forms aggregates,

or suffers some other adverse interaction making it unsuitable for use. Uda does not, therefore, provide any teaching or suggestion that benzethonium chloride would be an effective substitute for benzalkonium chloride in Strickland and, as stated above, Strickland specifically teaches away from making such substitutions.

Similarly, while Sandeep mentions that benzethonium chloride could be used as an antimicrobial, there is no teaching or suggestion that it would be a functional equivalent of benzalkonium chloride or that such a substitution would overcome the known problems of providing stable EPO multi-dose formulations. And again, as stated above, Strickland teaches away from making such substitutions.

As the Examiner has failed to establish a prima facie case of obviousness, Applicant respectfully requests that this rejection be withdrawn.

Claims 2-3, 6, 9-15, 21-22, 25, 28-33, 36-49, 55-56, and 62-68 are rejected under 35 U.S.C. § 103(a) as unpatentable over Strickland et al., Uda et al., and Sandeep et al. in further view of Hyman et al.

Strickland, Uda, and Sandeep have been discussed above and for the reasons stated, the Examiner has failed to establish a prima facie case of obviousness using those references. That deficiency is not cured by Hyman et al. which allegedly discloses that 9-aminoacridine hydrochloride and benzethonium chloride interact synergistically to inhibit *E. coli* growth. However, there is nothing in Hyman or any other cited reference to teach or suggest that combining benzethonium chloride with any other preservative would result in the synergistic effect described in the present application.

Further, as discussed previously, there is nothing in Hyman to suggest that such a combination could be used to create pharmaceutical compositions, particularly compositions

requiring maintenance of protein stability. Hyman supposedly discloses an antibacterial soap or detergent and contains no suggestion to any possible pharmaceutical use.

In addition, Hyman was published in 1970, thirty-two years before the present application was filed, twenty-seven years before Strickland and Sandeep, and twenty-six years before Uda. The fact that no other references from the intervening period of time teach a synergistic combination of benzethonium chloride with any other preservative further illustrates that such combinations were not obvious and merely combining benzethonium chloride with any other known antimicrobial would not have been likely to result in such a synergistic effect.

Finally, nothing in Sandeep or Uda teach or suggest that combining antimicrobials will result in a synergistic combination and certainly neither reference teaches any synergistic combinations that include benzethonium chloride. Once again, Strickland, as discussed above, actually teaches away from substituting such a combination to provide a stable, sterile, multi-dose EPO formulation.

As the Examiner has failed to establish a prima facie case of obviousness, Applicant respectfully requests that this rejection be withdrawn.

Claims 1, 4-8, 16-19, 35, 38-42, and 50-53 are rejected under 35 U.S.C. 102(a) as being unpatentable over Kakimoto et al. and Shimoda et al. (U.S. Patent No. 4,879,272) and Uda et al.

The Examiner asserts that Shimoda teaches a variety of additives to reduce adsorption of EPO to the walls of containers. The Examiner admits that Shimoda does not teach the use of benzethonium chloride to prevent such adsorption. In fact, Shimoda states that the substances disclosed in the reference "were found to be effective among the many substances that were checked for their ability to prevent the adsorption of erthropoietin on the inner surfaces of the walls of containers." Col. 2, lines 41-45. Further, Shimoda states that the exact mechanism by

which any of the disclosed substances prevent adsorption is not known. Col. 2, lines 45-48. Thus, Shimoda teaches that a small number of substances from "many substances that were checked" might be effective at preventing adsorption. But there is nothing in Shimoda to aid one of skill in the art in identifying additional substances since the mechanism is not known and certainly nothing in Shimoda would teach or suggest that benzethonium chloride could be used to prevent adsorption of EPO to container walls.

The Examiner further asserts that Kakimoto teaches the use of benzethonium chloride to prevent adsorption of proteins to container walls. But Kakimoto, as previously discussed only discloses preventing the adsorption of proteins with molecular weights of 200 to 6000 (p. 5, lines 18-26). Kakimoto does not teach or disclose that benzethonium chloride could be used to prevent adsorption of proteins the size of EPO, that is proteins five-fold larger than the range discussed. Kakimoto does not, as the Examiner asserts, teach or suggest that benzethonium chloride could be used to prevent adsorption of EPO to the walls of a container. Further, there is nothing in either Kakimoto or Shimoda that would teach or suggest any functional relationship between benzethonium chloride and any of the substances disclosed in Shimoda.

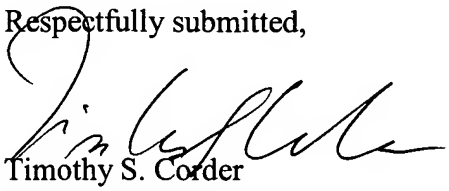
Finally, the Examiner further relies on Uda to provide the teaching that benzethonium chloride was a known antimicrobial. For the reasons discussed above, however, Uda does not provide any teaching or suggestion to demonstrate that benzethonium chloride could be used as an effective antimicrobial for stable, sterile, multi-dose EPO compositions. There is also no teaching or suggestion in any of these references to suggest that if they were combined, that such a combination would result in the claimed compositions.

As the Examiner has failed to establish a prima facie case of obviousness, Applicant respectfully requests that this rejection be withdrawn.

Conclusion

Applicant submits that, based on the Amendments and Remarks herein, the claims are in condition for allowance and such favorable action is respectfully requested. If the Examiner has any questions or comments that might accelerate allowance of these claims, he is invited to contact the undersigned representative at (512) 542-8530.

Respectfully submitted,



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